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Hormone Replacement Therapy and Breast Cancer Risk

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13. ABSTRACT (Maximum 200 Words) Hormone replacement therapy (HRT) use is associated with a small increased risk of developing breast cancer. Currently, it is not possible to predict which women using HRT are at increased risk of developing breast cancer. HRT causes an increase in mammographic density in 17-37% of women. Women with increased mammographic density are also known to be at increased risk for developing breast cancer. We therefore hypothesize that women who have an increase in mammographic density in response to HRT. The purpose of this case-control study is to determine if an increase in mammographic density in response to HRT is associated with an increased risk of breast cancer. Breast cancer cases at our institution between 1990-2000 will be evaluated, identifying postmenopausal women using HRT at the time of diagnosis. These women will be matched (1:2, case: control) by age and year of mammogram. Clinical data will be collected. Change in breast density over time will be assessed using quantitative digital analysis. Odds ratios will estimate the association between HRT-associated increase in breast density and risk of breast cancer.				
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INTRODUCTION:

Hormone replacement therapy (HRT) slows bone loss and improves quality of life for many women, but its use is also associated with a small increased risk of developing breast cancer (1-3). The estrogen plus progesterone arm of the Women's Health Initiative recently closed due to the increased risk of breast cancer without a benefit in prevention of cardiovascular disease or stroke (4). Many women will still choose to use HRT to treat hot flashes and to improve perceived quality of life despite the small increase in breast cancer risk. Currently, it is not possible to predict which women using HRT are at increased risk of developing breast cancer. On the mammogram, HRT is known to slow the normal involution of the breast and causes an increase in mammographic density in 17-73% of women (Figure 1) (5-8). This effect is more common with use of estrogen with progestin compared to estrogen alone (7). Women with increased mammographic density are also known to be at increased risk for developing breast cancer (9). We therefore hypothesize that women who have an increase in mammographic density in response to HRT are at higher risk for developing breast cancer than those women who do not have a change in mammographic appearance in response to HRT.

The purpose of the work funded by this grant is to determine if an increase in mammographic breast density in response to HRT is associated with an increased risk of breast cancer.

The overall goals of the project, as stated in the original application, are to:

- 1) Determine the association between HRT-induced changes in breast density and incident breast cancer
- 2) Quantify the association between initiation and duration of HRT and subsequent change in breast density
- 3) Demonstrate the utility of digital quantitative techniques for determining and reporting breast density

BODY:

As taken from the original Statement of Work, the tasks scheduled to begin and/ or be completed during the project period are as follows:

Task 1. Identify potential cases (months 1 –6).

- List of 1340 women diagnosed with breast cancer at the University of Virginia between 1990 and 1999.
- Update patient listing of women with diagnosis of breast cancer at the University of Virginia (UVA) to include those diagnosed in 2000.
- Include: Postmenopausal by natural menopause or hysterectomy with bilateral oophorectomy, and using estrogen and progestin for at least one year.

- Exclude: Premenopausal or perimenopausal, history of hysterectomy without bilateral oophorectomy, HRT use prior to onset of natural menopause, use of estrogen alone, concurrent use of testosterone, women with implants, diagnosis of cancer prior to the index year.

Task 2. Identify potential controls (months 1 – 6).

- Use mammography database and radiology information system to identify controls
- Controls selected using same inclusion/exclusion criteria as cases.
- Controls will be frequency matched to cases in a 2 control: 1 case ratio by year of diagnosis, age (± 5 years), and time between pre- and post-HRT mammograms (± 6 months).

Task 3. Collect demographic and clinical data (months 7 – 12).

- Use medical records to obtain demographic data
- Collect age, time since menopause, duration of HRT use, parity, age at first childbirth, and height and weight to calculate Body Mass Index (BMI).

Task 4. Locate and select mammograms (months 7 – 12).

- Exclude women with mammograms from other institutions
- Anticipate locating films for approximately 122 cases
- Select pre-HRT mammogram (within one year prior to using HRT)
- Select post-HRT mammogram at least one year after onset of HRT use. Closest date will be used (within 5 years after onset of HRT use).

Task 5. Determine pre-HRT breast density, and the change in breast density with HRT use using digital assessment (months 13 - 18).

- Digitize pre- and post-HRT mammograms.
- Assess breast density of pre- and post-HRT mammograms using digital quantitative analysis to obtain the percentage of the breast occupied by breast tissue.
- Obtain the change in breast density by:

$$\begin{array}{l} \text{\% breast occupied} \\ \text{by breast tissue}_{\text{post-HRT}} \end{array} - \begin{array}{l} \text{\% breast occupied} \\ \text{by breast tissue}_{\text{pre-HRT}} \end{array} = \text{change in density}$$

Task 6. Analyze data and perform statistical analysis (months 19 – 24).

- Summarize patient characteristics for cases and control groups.
- Determine if these data provide evidence that women undergoing HRT who developed breast cancer are more likely to have an increase in mammographic breast density than those who did not develop breast cancer.

- Estimate the odds ratio and construct a 95% confidence interval around the point estimate with and without adjustment for confounding factors.

ACCOMPLISHMENTS:

In regards to Task 1, we have obtained lists of women diagnosed with breast cancer at UVA between 1991-2000 through our pathology department, via searching for both women who underwent mastectomy or lumpectomy during this time period. These lists are being cross-checked through our mammography biopsy database to ensure completeness of data collection. We have reviewed 1243 records to date. Of the reviewed cases, 1029 women have been excluded due to premenopausal or perimenopausal status, having no mammograms prior to cancer diagnosis at UVA, implants or other criteria as listed in Task 1. To date, we have identified 146 postmenopausal women using HRT at the time of cancer diagnosis. Of these, 69 used estrogen and progesterone. Sixty-one women using only estrogen at the time of diagnosis will be excluded. HRT type is unknown for 16 women; medical records will be checked to see if some of these were using estrogen and progesterone. The number of cases identified to date (women on both estrogen and progesterone at time of diagnosis) should give adequate power for the study.

Collection of control subjects took much longer than anticipated (Task 2). While some demographic data has been collected in our mammography database, it has been too inconsistent to be used reliably. We therefore decided to do manual matching of cases. For each case, we did a search of our mammography database to obtain a list of names of women of age ± 5 years at the same time as the case (± 1 month). The mammography charts were then pulled beginning at the top of the list until two eligible controls subjects were obtained. If no eligible control subjects were obtained, then a new search performed ± 2 months (protocol calls for ± 12 months), etc. until 2 control subjects were obtained. This process has been far more time intensive than originally planned. However, we have identified 2 control subjects each for 54 of our 69 women using estrogen and progesterone (cases) (2:1 matching). Our statistician has been instrumental in redesigning our matching process.

Clinical and demographic data have been collected on all cases to date as this has been done at the time of case ascertainment (Task 3).

We have already excluded women that do not have prior mammograms at UVA (Task 4), reducing the likelihood that the number of HRT users will be significantly further reduced. We have centralized patient film jackets of the HRT users to ease mammogram selection (Task 4). Mammograms are currently being digitized with about 25% completed.

Tasks 5 and 6 will be accomplished during the next year of this no cost extension. Prior to assessing the mammograms for a change in breast density for study cases and controls (Task 5), it has become apparent that a meaningful change in breast density must be defined. To this end, we selected 51 cases of postmenopausal women reported to have a change in breast density due to HRT use in 1997-2001. Ten control cases of

postmenopausal women with no change in density during the same time period were selected. Mammograms were digitized using a high-resolution Lumisys 75 scanner. Density was visually assessed by one radiologist experienced in breast imaging and classified as 0: No change, +1: Focal or minimal increase in density, +2: Moderate increase in density, and +3: Marked increase in density. Change in breast size and BIRADS density categories was also assessed. Digital assessment was performed using segmentation and interactive thresholding to obtain percent density.

Results: Of the 51 cases of postmenopausal women with increase in breast density associated with HRT use, 21 had a minimal increase in density, 16 had a moderate increase in density, and 14 had a marked increase in density. Radiologic characteristics of the increase in density are given in the table below.

Table 1. Radiologic characteristics of visual assessment of increase in density with HRT use.

Radiologic Characteristics	Visual Assessment			
	Minimal (N = 21)	Moderate (N = 16)	Marked (N = 14)	Total (N = 51)
Focal Increase	4 (19%)	0	0	4 (8%)
Diffuse Increase	17 (81%)	16 (100%)	14 (100%)	47 (92%)
Increase in breast size	0	0	14 (100%)	14 (27%)
BI-RADS assessment				
Same BI-RADS category	19 (90%)	0	0	19 (37%)
Increase by one BI-RADS category	2 (10%)	15 (94%)	8 (57%)	25 (49%)
Increase by two BI-RADS categories	0	1 (6%)	6 (43%)	7 (14%)

Given these results, use of only the BIRADS category to assess for a change in breast density, results in underestimation of 37% of HRT associated cases of breast density (19 women with no change in BIRADS category/51 total).

We have also evaluated these same 51 women with HRT associated increase in breast density using the digital segmentation and interactive thresholding technique. Using this technique, the percent density of each mammogram was obtained and the percent change in breast density calculated by subtracting the density of the first mammogram from the later mammogram (Table 2).

Table 2. Quantitative assessment of increase in breast density with visual assessment of density change

Visual Change	Percent Change, mean (range)	20 th Percentile Difference	80 th Percentile Difference
No change	+0.2% (-4.6 - +4.7%)	-2.6	2.6
Minimal Increase	+8.8% (+2.0 - +18.8%)	5.8	10.5
Moderate Increase	+19.1% (+13.4 - +26.8%)	14.3	22.5
Marked Increase	+39.2% (+20.9 - +54.8%)	28.1	49.4

Using this data, we propose the following scale for assessing a meaningful change in breast density:

Table 3. Proposed scale of visual and quantitative assessment of change in breast density.

Visual Assessment	Proposed Quantitative Scale ¹
No significant change	0 to 2.9%
Minimal Increase	3 to 14.9%
Moderate Increase	15 to 24.9%
Marked Increase	≥25%

¹ Percent increase in density

Application of this scale to our data set showed good agreement with a weighted kappa of 0.87.

Discussion: Previous studies assessing a change in breast density have used a visual assessment or changes in BI-RADS or Wolfe's categories. Those using visual assessment have not defined the degree of change, which may lead to variability between readers and studies. Use of change in BI-RADS or Wolfe's categories over time is more quantitative, but is a rather coarse assessment of change. In this study, we have defined changes in

breast density in clinically meaningful visual categories. Furthermore, we have correlated these cases with digital assessment of percent change in density to further quantify a meaningful change in density. Since our study may show that changes in mammographic density may signify changes in breast cancer risk, these definitions may be useful for quantifying the percentage of women with minimal, moderate, and marked changes in breast density due to different stimulatory or preventive hormonal regimens.

The above results will be used in our study analysis, by defining a significant change in breast density as $>3\%$.

KEY RESEARCH ACCOMPLISHMENTS:

- Reviewed 1243 records, obtaining 69 cases of women using estrogen and progesterone at the time of cancer diagnosis that meet inclusion criteria.
- Women without prior mammograms at UVA have already been excluded decreasing the likelihood of further case exclusions.
- Clinical data has been obtained on all collected cases to date.
- Identified 2 control subjects for 54 of the above 69 cases to date.
- Digitized about 25% of mammograms
- Established a scale of clinically meaningful change in breast density for women using HRT by visual and digital assessment techniques.

REPORTABLE OUTCOMES:

Scientific Presentations:

Harvey JA, Williams MB, Petroni G, Bovberg V. Increasing Mammographic Breast Density in Response to Hormone Replacement Therapy and Breast Cancer Risk. The Department of Defense Breast Cancer Research Program Meeting: Era of Hope, September 25-28, 2002, Orlando, Florida. (preliminary data presented)

Harvey JA, Williams MB, Petroni G, Bovberg V. Establishing a Scale of Clinically Meaningful Change in Breast Density in Women using Hormone Replacement Therapy Using Visual and Digital Assessment Techniques. 25th Annual San Antonio Breast Cancer Symposium, December 11-14, 2002, San Antonio, Texas. (preliminary data presented)

Publications:

Harvey JA, Petroni G, Smolkin M, Williams MB, Bovberg V. Comparison of Visual Assessment and BI-RADS categories for Evaluating Hormone Replacement Therapy Associated Increase in Mammographic Breast Density (in preparation).

Harvey JA, Petroni G, Smolkin M, Williams MB, Bovberg V. Quantitative Assessment of Hormone Replacement Therapy Associated Increase in Mammographic Breast Density (in preparation).

CONCLUSIONS:

We have reviewed available breast cancer cases at UVA and obtained a reasonable number of cases of postmenopausal women using estrogen and progesterone at the time of cancer diagnosis. The cases accrued are already known to have prior mammograms at our institution. Control subjects have been identified for the majority of the cases (2:1 matching). Mammograms are in the process of being digitized. In order to perform the density assessment, we developed a scale of meaningful change in breast density for women using HRT, which will aid in our data analysis.

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APPENDICES:

Publications in preparation (final editing not complete!):

Harvey JA, Petroni G, Smolkin M, Williams MB, Bovberg V. Comparison of Visual Assessment and BI-RADS categories for Evaluating Hormone Replacement Therapy Associated Increase in Mammographic Breast Density (in preparation).

Harvey JA, Petroni G, Smolkin M, Williams MB, Bovberg V. Quantitative Assessment of Hormone Replacement Therapy Associated Increase in Mammographic Breast Density (in preparation).

**Comparison of Visual Assessment and BI-RADS categories for Evaluating
Hormone Replacement Therapy Associated Increase in Mammographic
Breast Density** *(manuscript in preparation)*

Comparison of Visual Assessment and BI-RADS categories for Evaluating Hormone Replacement Therapy Associated Increase in Mammographic Breast Density

Abstract:

Increased mammographic breast density associated with use of hormone replacement therapy (HRT) is common although the reported incidence is widely variable likely due in part to lack of standardized assessment. The purpose of this work is therefore to evaluate mammograms of postmenopausal women with HRT associated increases in density using mammographic characteristics and BI-RADS density categories, and to subsequently develop a defined visual scale for assessing HRT associated increases in breast density. The mammograms of 51 postmenopausal women reported to have an HRT associated increase in breast density and 20 postmenopausal women with no density change were evaluated using visual assessment, focal versus diffuse change, increase in breast size, and BI-RADS categories. The defined visual scale developed consists of: no change; minimal increase corresponding to a focal increase or diffuse increase with no change in BI-RADS category or breast size; moderate increase corresponding to an increase of one BI-RADS category without an increase in breast size; marked increase corresponding to an increase of one or more BI-RADS categories with an associated increase in breast size. In this series, 37% of all cases of HRT associated increase in breast density would be

misclassified if BI-RADS category change alone was used to assess for change in density.

The defined visual scale developed in this study may be more sensitive and reproducible for quantifying the percentage of women with increases in breast density due to different hormonal regimens than use of BI-RADS density categories alone.

The abbreviations used are: HRT, hormone replacement therapy; BI-RADS, Breast Imaging Reporting and Data System

The U.S. Army Medical Research Materiel Command under DAMD17-01-1-0042 supported this work.

Comparison of Visual Assessment and BI-RADS categories for Evaluating Hormone Replacement Therapy Associated Increase in Mammographic Breast Density

Introduction

There is increasing interest in the effect of specific agents on breast density since the number of women exhibiting changes in density and their degree of change may imply changes in breast cancer risk. HRT use increases breast cancer risk (6-8) and increases breast density (1-5, 24-26); both are more significant with use of combined estrogen and progesterone compared to estrogen alone (1, 2, 5, 24,25, 6-8). The estrogen plus progestin arm of the Women's Health Initiative recently closed due to the increased risk of breast cancer without a benefit in prevention of cardiovascular disease or stroke while the estrogen alone arm remains open (9). In contrast, use of tamoxifen is associated with a 50% reduction in breast cancer risk in high-risk women (20), and is associated with a decrease in breast density in 44% of women (21). Raloxifene use likewise reduces breast cancer risk by 75% in average risk women (22), and is also associated with a decrease in breast density (19). Thus, change in breast density with use of hormonal agents may be a surrogate marker for breast cancer risk.

The percentage of women that experience an HRT associated increase in density is widely variable however, reported in 17-73% of women (25, 3). This wide range is likely due to differences between regimens and methods of

assessing change. Of the studies with at least 30 cases, 17-73% of women using estrogen and progesterone (25, 3) and 3.5- 5.0% of women using estrogen alone are reported to have an increase in breast density (2, 5). Some variability in effect may also be due to administration route, type of estrogen (conjugated equine estrogen, estradiol), type of progestin (medroxyprogesterone, micronized progesterone, nor-progestins), and if progesterone is administered continuously or only part of the month. Considerable variability is still seen within similar regimens and is likely due different methods of assessing density change.

Prior studies assessing changes in density in association with HRT use have used either visual assessment with a yes/no response (24, 25), visual scale of change (2), or change in Breast Imaging Reporting and Data System (BI-RADS) (10) density category (5, 4) or Wolfe criteria (3, 23) to evaluate for changes in breast density. Use of a binary response (yes/no) lacks a defined threshold of change that was called positive. Use of a visual scale to assess change in density adds quantitative information, but may not be reproducibed if categories are not defined. A change in BI-RADS breast density category or Wolfe criteria also adds some degree of quantitative assessment, although these categories are not quantitatively defined resulting in low intra- and inter-reader agreement (kappa 0.43 to 0.59) (11, 12). Thus, assessment of reported changes in BI-RADS density category could be due to reader variability rather than a true change in density in a substantial proportion of women. In addition, women with a small

increase in density may still remain in the same BI-RADS density category, resulting in underestimation of HRT associated increase in density.

Quantitative assessment of breast density at an individual point in time has been performed using visual (13, 14) or digital assessment (15-17) with good reproducibility (15, 18). While much work has recently been done in quantitative assessment of mammographic breast density because of the moderate association of high breast density with breast cancer risk (15-17), use of digital assessment has been infrequently used for assessing changes in density due to use of hormonal agents (19, 26).

Given the wide variability in reporting of HRT associated increase in mammographic breast density, we evaluated selected mammograms exhibiting increased breast density associated with HRT use by visual assessment and by BI-RADS categories, and developed definitions for a visual scale that could be used to assess an HRT associated increase in breast density.

Methods and Materials

At our institution, observed increases in mammographic breast density secondary to HRT use are noted in the mammogram report. Using this information in our computerized database, we identified 51 postmenopausal women during 1997-2001 with increased breast density associated with HRT use. Twenty postmenopausal women with no reported change in density during

the same time period were selected for comparison. Both the mammogram noting a change in density and a preceding mammogram were digitized using a high-resolution Lumisys 75 scanner at 8-bit depth, 2K by 2.8K, optical density range 0.0-3.8, and 72 pixels per inch. Images were reduced in size (12 inch height) in order to view the entire image on the monitor. The preceding baseline mammogram for cases was the one compared to in the mammography report noting the interval increase in breast density. For controls, the baseline mammogram was selected as 1 to 5 years before the index mammogram depending upon what was available for each patient. An interval of two or more years was preferred to a one year interval as this is our standard when interpreting mammograms at our institution. Only the left craniocaudal views were used to assess density since one view has been shown to be accurate for assessing breast density (18). Visual assessment was performed by one radiologist (JAH) with 10 years of experience in breast imaging. Readings were performed in a blinded fashion without knowledge of whether a change in breast density had been reported or not. Baseline and index mammograms were compared side by side on a monitor with the older mammogram on the left and the more recent mammogram on the right.

Visual assessment

Change in density was assigned as none, minimal, moderate, or marked interval increase. Specific radiologic changes were assessed including whether the increase in density was focal or diffuse and if there was a corresponding interval

increase in breast size. BI-RADS breast density categories were assigned for the baseline and index mammograms. BI-RADS density categories are defined as: almost entirely fat, scattered fibroglandular densities, heterogeneously dense, and extremely dense (10). The above characteristics were then used to define a visual scale of change in breast density associated with HRT use.

Statistical analysis

Frequencies and summary measures of baseline characteristics including age and breast density were calculated. All possible pairwise comparisons were generated in order to assess overlap among the four categories. Weighted kappa statistics and 95% confidence intervals were used to assess agreement between the initial visual assessment rating and the proposed visual scale.

Results

Age and baseline breast density were similar between those with and without changes in breast density (Table 1). The time interval from baseline to index mammogram was significantly shorter for those with HRT change in breast density than control patients (22.4 versus 30.6 months respectively, $p=0.008$).

Visual assessment of change in mammographic breast density of the 51 women reported as having an increase in breast density associated with HRT use resulted in assignment of 21 cases to minimal increase (+1), 16 cases to moderate increase (+2), and 14 cases to marked increase in breast density (+3)

(Figure 1). The 20 women with no report of change in breast density were all assessed as category 0: No change.

Mammographic Characteristics of Increasing Breast Density

HRT associated increase in breast density was focal in 4 patients (8% of patients with an increase in breast density) and diffuse in 47 (92% of patients with an increase in breast density) (Table 2). All four patients with focal increase in breast density were considered to have minimal increases in breast density. Overall increase in breast size was noted in 14 women (27% of women with an increase in breast density), who were all considered to have a marked increase in breast density.

In the 51 cases judged by visual assessment to have an increase in breast density, the degree of increase in breast density was also assessed using BI-RADS categories. Nineteen patients had no change in BI-RADS category (37%), 25 had an increase of one BI-RADS category (49%), and 7 had an increase of two BI-RADS categories (14%)(Table 3). All cases with a moderate or marked increase in density had an increase of at least one BI-RADS category (Table 2), although only 2 of the 21 women (10%) with minimal change had an increase in BI-RADS category.

Definitions for Visual Scale of Assessing Increases in Breast Density

For those judged to have minimal increases in breast density, the dominant features were diffuse increase in density (81%), no change in BI-RADS density category (90%), and no increased breast size (100%)(Table 2). While less common, focal increase in density was very specifically related to minimal increase in density, as all four women with focal change were considered to have minimal increase in density.

For those judged to have a moderate increase in breast density, the dominant features were diffuse increase in density (100%), increase of one BI-RADS density category (94%), and no increased breast size (100%). Only one patient judged to have a moderate increase in density changed by two BI-RADS categories (6%). For those judged to have marked increases in density, the dominant features were diffuse increase in density (100%), increase of one (57%) or two (43%) BI-RADS categories, and increased breast size (100%).

The dominant findings of minimal, moderate, and marked increase in density given above were used to develop definitions for a visual scale incorporating BI-RADS categories, but not relying solely upon their use (Table 4). The additional radiographic information of focal versus diffuse change and increase in breast size were also incorporated. Using the visual scale with these definitions, only 2 of the 51 cases (4%) would be classified differently from the initial visual reading (Table 5) (weighted kappa of 0.98, 95% CI: (0.94,1.0)). **SEE VIKTOR'S NOTE**

Comparison of Defined Visual Scale with use of BI-RADS categories

If BI-RADS categories alone were used to assess for HRT-induced increase in breast density, then 90% of cases with minimal increase in density would be classified as not having density changes. In this series, this would result in misclassification of 37% of all cases of HRT induced increase in breast density if BI-RADS category change alone were used to assess for change in density.

Assessing an increase in breast density by using the BI-RADS categories alone can also be difficult when the baseline density is already moderate or extreme, as the maximal increase can only be by one category (moderate to extremely dense). In this study, 5 of the 14 women (36%) with marked increases in breast density changed from heterogeneously moderately dense to extremely dense. These women would be considered to have a moderate increase in density if BI-RADS categories alone were used. In contrast, an increase of two BI-RADS categories identified fewer than half of those with a marked increase in breast density by visual assessment. Assessment of density change using BI-RADS categories alone will be limited, particularly for women whose baseline mammogram is already heterogeneously or extremely dense.

Discussion

Assessment of change in breast density has been limited by lack of a consistent reproducible method. Current methods use either a visual assessment with

yes/no binary response () or scale (), or change in BI-RADS () or Wolfe criteria (). Quantitative digital assessment is possible, but not widely used.

Visual assessment of density change is useful for detecting a wide range of change. Persson et al used a visual scale defined as moderate or slight decrease in density, no change, or slight, moderate, or marked increase in density to evaluate mammograms of 554 women using HRT and 554 women not using HRT (2). The categories were not otherwise defined. This study found that most increases in density were slight. Overall, 66% of women using HRT with an increase in density in this study were considered to have a slight increase. Thus, use of a visual scale detects and quantifies small and large increases in density. However, lack of definition of criteria for a visual scale, as in the study by Persson et al, may limit reproducibility. In this study, we used a combination of mammographic characteristics and BI-RADS category changes to develop definitions for a visual scale that had excellent correlation with our initial visual assessment. Reproducibility assessment of this scale is currently underway.

Because of the widespread use of BI-RADS terminology in the United States, assessing large populations for changes in breast density using change in BI-RADS density category is very practical. Pre-existing BI-RADS density category data from large populations could be evaluated very efficiently without reanalyzing the mammograms. However, assessment of change in density using

change in BI-RADS density category is limited in the detection of small changes in density, reproducibility, and ability to quantify change.

Use of BI-RADS categories to assess change in density is limited for those with small changes in mammographic breast density. In our series, 37% of women with visually assessed increase in breast density associated with HRT use would be excluded if a change in BI-RADS category were the sole criteria for assessing change. Likewise, in the study by Persson et al, 66% of women with a visually assessed change in breast density had only a slight increase. Many of these may have been excluded if BI-RADS categories had been used rather than visual assessment.

The accuracy of use of BI-RADS categories to assess change in density is also limited by intra- and inter-reader variability. Assignment of a subsequent mammogram to a different BI-RADS category may be due to reader variability rather than a true change in breast density. Rutter et al used BI-RADS categories as well as quantitative digital assessment to assess changes in breast density with initiation, continued, and discontinuation of HRT (4). In this study, women whose baseline and 12-month mammogram were both minimally dense by BI-RADS category had a range of change of -25% to +27% by quantitative methods. Likewise, women whose baseline mammogram was considered fatty and the 12-month mammogram increased to minimally dense by BI-RADS categories had a range of increase of 0.5% to 38%. These findings suggest that

use of BI-RADS categories alone to assess change will yield only a rough estimate. However, the study by Rutter, et al, evaluated 5212 postmenopausal women and performing visual assessment of density change of more than 5000 pairs of mammograms would be impractical.

Use of the BI-RADS density categories also does not quantify change well. In our case group, 90% of those with a visually determined minimal increase in breast density would have been considered to have no change in breast density if only BI-RADS categories had been used. Likewise, if an increase of two BI-RADS categories is used to assess women with marked increase in breast density, then less than half of the women that were actually considered to have a marked increase in density by visual assessment would have been included. Thus, use of the BI-RADS density categories will be limited in its sensitivity for detecting and quantifying changes at the lower and upper ends of the spectrum.

Quantitative digital assessment of percent breast density will become more useful as digital mammography becomes more widespread. Currently analog mammograms must be digitized before quantitative assessment can be performed, which becomes cumbersome with large numbers of mammograms.

The use of a defined visual scale may more effectively and reproducibly detect increases in breast density in association with HRT use. Change in BI-RADS

categories may be the only practical method to evaluate very large populations with preexisting data.

A limitation of our study is validation of the defined visual scale by other readers, which is now underway. Our study is limited by potential selection bias as our series consists of women reported to have increases in density and an unknown additional number of women may also have exhibited an increases in density during this time period. Further studies using consecutive patients will be necessary to evaluate the full spectrum of HRT change in a series of representative patients. Because this study is based on a single sample, it will likely show greatest concordance in this group. To assess whether this scale is useful, application to a new sample would be needed to assess generalizability.

This study demonstrates that minimal, moderate, and marked visual increase in breast density associated with HRT use correspond to focal increase or diffuse change of less than one BI-RADS category, an increase in density of one BI-RADS category without an increase in breast size, and an increase of one or more BI-RADS categories with an associated increase in breast size respectively. Use of BI-RADS categories alone, while practical for evaluating large populations, results in underestimation of small and large increases in density and is limited by significant reader variability. The defined visual scale developed in this study may be useful for quantifying the percentage of women

with minimal, moderate, and marked changes in breast density due to different hormonal regimens, which may have implications for breast cancer risk.

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Figure 1. Visual Assessment of Change in Breast Density Categories.

Craniocaudal views of the left breast are shown before (A1, B1, C1) and 1-2 years after (A2, B2, C2) initiation of HRT. Case A illustrates a minimal increase in density with the breast density increasing diffusely, but both mammograms are in the heterogeneously moderately dense category. Case B illustrates a moderate increase in density with scattered fibroglandular elements initially and moderately dense tissue following initiation of HRT. Case C illustrates a marked increase in density with scattered fibroglandular elements initially and heterogeneously moderately dense tissue with a significant overall increase in size of the breast after initiation of HRT.

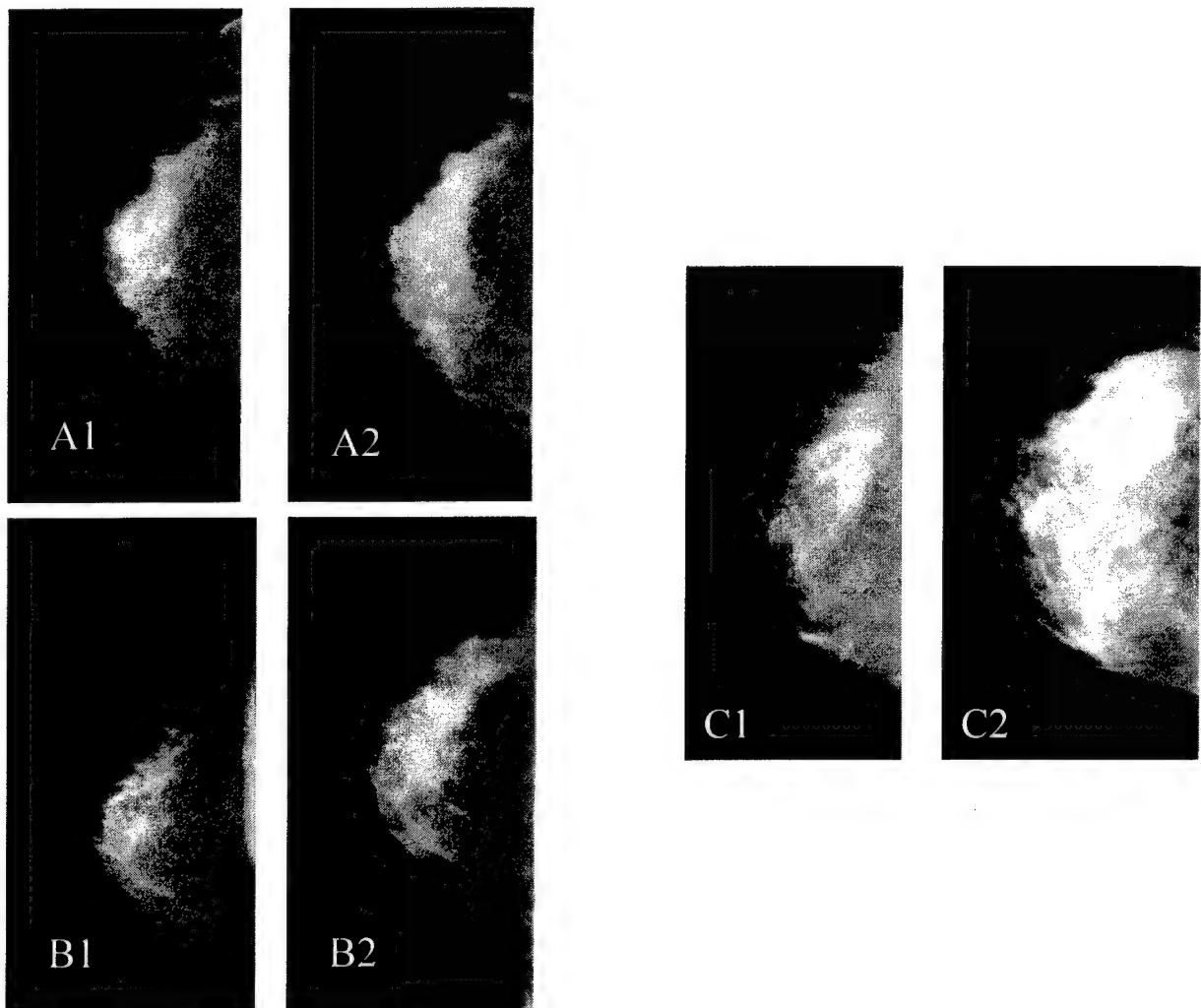


Table 1. Baseline characteristics of the study population

	HRT-induced Increase in Density (N = 51)	No Change in Density (N = 20)
Age (years) (mean, range)	59.6 (41 - 77)	60.3 (49 - 74)
Interval from baseline to index mammogram (months) (mean, range)	22.4 (11.5 - 59.6)	30.6 (12.4 - 59.3)
Baseline Parenchymal Pattern		
Fatty	9/51 (18%)	4/20 (20%)
Scattered	28/51 (55%)	7/20 (35%)
Heterogeneous	13/51 (25%)	8/20 (40%)
Extremely dense	1/51 (2%)	1/20 (5%)

Table 2. Radiologic characteristics of visual assessment of increase in density with HRT use.

Radiologic Characteristics	Visual Assessment			
	Minimal (N = 21)	Moderate (N = 16)	Marked (N = 14)	Total (N = 51)
Focal Increase	4 (19%)	0	0	4 (8%)
Diffuse Increase	17 (81%)	16 (100%)	14 (100%)	47 (92%)
Increase in breast size	0	0	14 (100%)	14 (27%)
BI-RADS assessment				
Same BI-RADS category	19 (90%)	0	0	19 (37%)
Increase by one BI-RADS category	2 (10%)	15 (94%)	8 (57%)	25 (49%)
Increase by two BI-RADS categories	0	1 (6%)	6 (43%)	7 (14%)

Table 3. Change in breast density as evaluated by BI-RADS density categories

	Index Mammogram Density			
	Fatty	Scattered	Heterogeneously Moderately Dense	Extremely Dense
Baseline Density				
Fatty	0	6	3	0
Scattered		10	14	4
Heterogeneously Moderately Dense			8	5
Extremely Dense				1

Table 4. Defined scale of visual assessment of increases in breast density.

Definitions for Visual Scale	
No change	No significant change
Minimal Increase	Focal increase or diffuse increase but of less than one BI-RADS category and no increase in breast size
Moderate Increase	Increase of one BI-RADS category with no increase in breast size
Marked Increase	Increase of one or more BI-RADS categories with an associated increase in breast size

Table 5. Agreement of initial visual assessment with proposed visual scale.

Defined Visual Scale	Initial Visual Assessment			
	No Change	Minimal	Moderate	Marked
No Change	20 (28.2%)			
Minimal		19 (26.8%)	2 (2.8%)	
Moderate			16 (22.5%)	
Marked				14 (19.7%)

**Quantitative Assessment of Hormone Replacement Therapy Associated
Increase in Mammographic Breast Density**

(manuscript in preparation)

Quantitative Assessment of Hormone Replacement Therapy Associated Increase in Mammographic Breast Density

Abstract:

An increase in mammographic breast density with use of hormone replacement therapy (HRT) is common and may reflect an increase in breast cancer risk. However, previous studies evaluating changes in density used either a yes/no response or a change in category. The purpose of this work is to establish a scale defining changes in density for women using HRT using both visual and digital techniques. The mammograms of 51 postmenopausal women reported to have an HRT-induced increase in breast density were evaluated using visual and digital technique. Twenty postmenopausal women with no change in density were selected as controls. Visual assessment corresponded to digital assessment as: minimal, moderate, and marked increase had a mean increase of 8.8% (range, 2.0 to 18.8%), 19.1% (range, 13.4 to 26.8%), and 39.2% (range 20.9 to 54.8%) respectively. The control group had a mean increase of 0.2% (range, -4.6 to +4.7%). Using this information, criteria for a visual and digital scale of change were developed. The visual scale is defined as: minimal change is a focal increase or diffuse increase, but less than a BI-RADS category; moderate change is an increase of one BI-RADS category without a change in breast size; marked change is an increase of one or more BI-RADS categories with an associated increase in breast size. These correspond to a 4 to 14.9%, 15 to 24.9%, and 25% or greater increase in density using digital technique. The

scales developed in this study may be useful for quantifying the percentage of women with minimal, moderate, and marked changes in breast density due to different hormonal regimens, which in turn may have implications for breast cancer risk.

The abbreviations used are: HRT, hormone replacement therapy; BI-RADS, Breast Imaging Reporting and Data System

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Quantitative Assessment of Hormone Replacement Therapy Associated Increase in Mammographic Breast Density

Introduction

There is increasing interest in the effect of specific hormonal agents on breast density since the number of women exhibiting an increase in density and their degree of change may imply a change in breast cancer risk. For example, use of tamoxifen is associated with a 50% reduction in breast cancer risk in high risk women (19), and is associated with a decrease in breast density in 44% of women (20). Raloxifene use likewise reduces breast cancer risk by 75% in average risk women (21), and is also associated with a decrease in breast density (22). In contrast, HRT use increases breast cancer risk (6-8) and increases breast density (1-5); both are more significant with use of estrogen and progesterone compared to estrogen alone (2, 5-8). Thus, change in breast density with use of hormonal agents may be a surrogate marker for breast cancer risk.

However, prior studies evaluating change in density with hormonal agents have had variable results, with 17-74% of women using HRT demonstrating an increase in breast density (1 - 4). These studies used visual assessment with a yes/no response (1-4), which lacks a defined threshold of change that was called positive, and likely explains some of the variability among these studies. One study has used a change in the Breast Imaging Reporting and Data System (BI-

RADS) (10) density category (5), which adds some degree of quantitative assessment. While use of change in BI-RADS categories is an efficient method for evaluating preexisting data, the intra- and inter-reader agreement of assignment of BI-RADS density categories is low (kappa 0.43 to 0.59)(11, 12) implying that assessment of reported changes in density category could be due to reader variability rather than a true change in density in a substantial proportion of women. Our prior work has shown that use of BI-RADS categories alone to assess an increase breast density associated with HRT use would exclude 37% of women that had an increase in breast density ().

Quantitative assessment of breast density at a single point in time has been performed using visual (13, 14) or digital assessment (15-17) with good reproducibility (15, 18). While much work has been done in quantitative assessment of mammographic breast density because of the implications for breast cancer risk (15-17), use it has been infrequently used for assessing a change in density due to use of hormonal agents (19).

In this study, we evaluated selected mammograms exhibiting an HRT associated increase in breast density using quantitative assessment by digital interactive thresholding technique and correlate with visual change ().

Methods and Materials

At our institution, we typically report an increase in mammographic breast density associated with HRT use. Using this information in our computerized database,

we identified 51 postmenopausal women reported to have an increase in breast density due to HRT use from 1997-2001. Twenty postmenopausal women with no reported change in density during the same time period were selected for comparison. Both the mammogram noting a change in density and a preceding mammogram were digitized using a high-resolution Lumisys 75 scanner at 8-bit depth, 2K by 2.8K, and 72 pixels per inch. Images were reduced in size (12 inch height) in order to view the entire image on the monitor. The preceding baseline mammogram for cases was the one compared to in the mammography report noting the interval increase in breast density. For controls, the baseline mammogram was selected as 1 to 5 years before the index mammogram depending upon what was available for each patient. A two year or longer interval was preferred to a one year interval as this is our standard when interpreting mammograms at our institution. Only the left craniocaudal views were used to assess density since one view has been shown to be accurate for assessing breast density (18). Baseline and index mammograms were compared side by side on a monitor with the baseline mammogram on the left and the index mammogram on the right. All readings were performed in a blinded fashion without knowledge of whether a qualitative change in breast density had been reported or not.

These mammograms were evaluated visually for HRT associated increase in breast density and quantified as no change or minimal, moderate, or marked increase in breast density as part of an earlier study (19). In the previous study, 21

cases (41%) were found to have a minimal increase in density as defined by focal increase or diffuse increase of less than a BI-RADS category, 16 cases (31%) had a moderate increase in density as defined as a diffuse increase of one BI-RADS category without an increase in breast size, and 14 cases (27%) had a marked increase in density as defined as a diffuse increase in breast density of 1 or more BI-RADS categories with an associated increase in breast size. All 20 control cases showed no change in density by visual assessment.



Quantitative assessment

Quantitative assessment of the mammograms was performed using a digital segmentation and interactive thresholding program developed by Yaffe et al (18) to obtain the percentage of the image occupied by breast tissue (percent density) (Figure 1). Change in breast density was obtained by subtracting percent density on the baseline mammogram from that on the index mammogram. The quantitative assessment was performed at least two weeks after the visual assessment by one radiologist (JAH) with 10 years of experience in breast imaging and two years of experience using the digital interactive thresholding software program. Results of quantitative assessment were correlated with the original visual assessment to define a quantitative scale of change in breast density associated with HRT use.

Statistical analysis

Frequencies and summary measures of baseline characteristics including age and baseline breast density were calculated. Linear regression models were used to examine the relationship between quantitative assessment of breast density and the four visual assessment categories. All possible pairwise comparisons were generated in order to assess overlap among the four categories. Weighted kappa statistics and 95% confidence intervals were used to assess agreement between the visual assessment rating and proposed digital scale.

Results

Age and baseline breast density were similar between those reported to have a change in breast density associated with HRT use and those with not reported to have a change in breast density (Table 1). HRT associated increase in breast density ranged from an increase of 2.0% in one patient with a very focal increase in density (Figure ) to an increase of 54.8% in a patient with a very obvious mammographic change (Figure )

Quantitative assessment of breast density corresponded well with visual assessment (Table 2). As shown in the boxplots, minimal overlap in percent change by quantitative assessment was observed between visual assessment change categories (Figure 2). All pairwise comparisons were statistically significant ($p < 0.001$).

Of the 21 patients with +1 increase in density by visual assessment, four patients had a focal increase which corresponded to a significantly lower percent change in density (mean 4.0% increase, range 2.0-5.8) compared to those with a minimal diffuse increase (mean 9.9% increase, range 5.6-18.8) ($p=0.009$).

Given the results of the quantitative assessment, we developed a scale for assessment of HRT associated increase in density (Table 3). Using the proposed scale, the correlation with visual assessment is very good (weighted kappa 0.87, 95% CI 0.80 – 0.95). No cases differed by more than one category between the visual and proposed digital scale (Table 4).

Discussion

To our knowledge, this is the first study attempting to quantify the degree of increase in breast density associated with HRT use. The results show a broad range of change, varying from 2-54% increase in density. The positive correlation of increase in breast density with HRT and breast cancer risk, and the negative correlation of breast density with agents that act as anti-estrogens in the breast, such as tamoxifen and raloxifene, suggest that changes in breast density may indicate subsequent breast cancer risk. The higher proportion of women exhibiting an increase in breast density associated with use of estrogen and progesterone compared to women using estrogen alone mirrors the greater breast cancer risk with combined HRT. These suggest that HRT regimens

affecting mammographic density in fewer women may have lower breast cancer risk than regimens that affect an increase in many women.

Independent of HRT use, postmenopausal women with very dense breast tissue on the mammogram are at 4-7 fold-increased risk for developing breast cancer (). Of interest is that not all women increase in breast density in association with HRT use. It is not known if women that have a large increase in density in association with HRT use are at greater risk for development of breast cancer than women that do not change in density. It may therefore be useful to quantify change in individual patients undergoing HRT and follow over time to correlate change in density with subsequent breast cancer risk.

Previous studies assessing an increase in breast density associated with use of HRT used visual assessment with a yes/no response (1-4) or changes in BI-RADS (5) or Wolfe's categories (23), yielding variable results. Because of the widespread use of BI-RADS terminology in the United States, it may be useful in assessing large populations for changes in breast density to avoid the time and expense of analyzing the mammograms. However, our previous work has shown that use of BI-RADS categories to assess change in density will be limited for those with small or large changes in mammographic breast density, nor does it quantify change well. In addition, low inter-reader agreement in assigning BI-RADS categories introduces considerable noise. Thus, although use of BI-RADS breast density categories may be an efficient method for analyzing preexisting

data, use of the BI-RADS density categories will be limited in its sensitivity for detecting changes, particularly at the lower and upper ends of the spectrum.

While this study evaluated change in density using digitized analog mammograms, quantitative assessment of breast density may be an ideal application for digital mammography given that the mammogram is already in digital format. The process would still be somewhat cumbersome as current quantitative methods still require a radiologist or technologist to perform the analysis. However, several investigators are developing automated measurement of breast density using segmentation of the mammogram with 80-90% agreement with visual quantitative assessment (38-40). Automated measurement of breast density would allow widespread use of quantitative assessment.

In this study, we quantified HRT associated increase in breast density and developed a quantitative scale, which showed very good association with visual assessment. A limitation of our study however is validation of this scale by other readers, which is now underway. Another limitation of this study is that this proposed scale is based on a single sample, and will therefore likely show greatest concordance in this group. To assess whether these scale is useful, application to a new sample would be needed to assess generalizability.

This study demonstrates that minimal, moderate, and marked visual increase in an increase of 3 to 14.9%, 15 to 24.9%, and 25% or greater increase in density. These definitions may be useful for quantifying the percentage of women with minimal, moderate, and marked changes in breast density due to different hormonal regimens, which may have implications for breast cancer risk.

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Figure 1. Digital assessment of breast density (18). The craniocaudal view is digitized (A). The skin and pectoral muscle lines are drawn to define the total breast area (B). A histogram of the densities in the region of interest is used to select the pixels corresponding to breast tissue (C). The number of pixels corresponding to breast tissue is divided by the number of pixels representing the total breast area and multiplied by 100 to obtain the % of breast occupied by breast tissue.

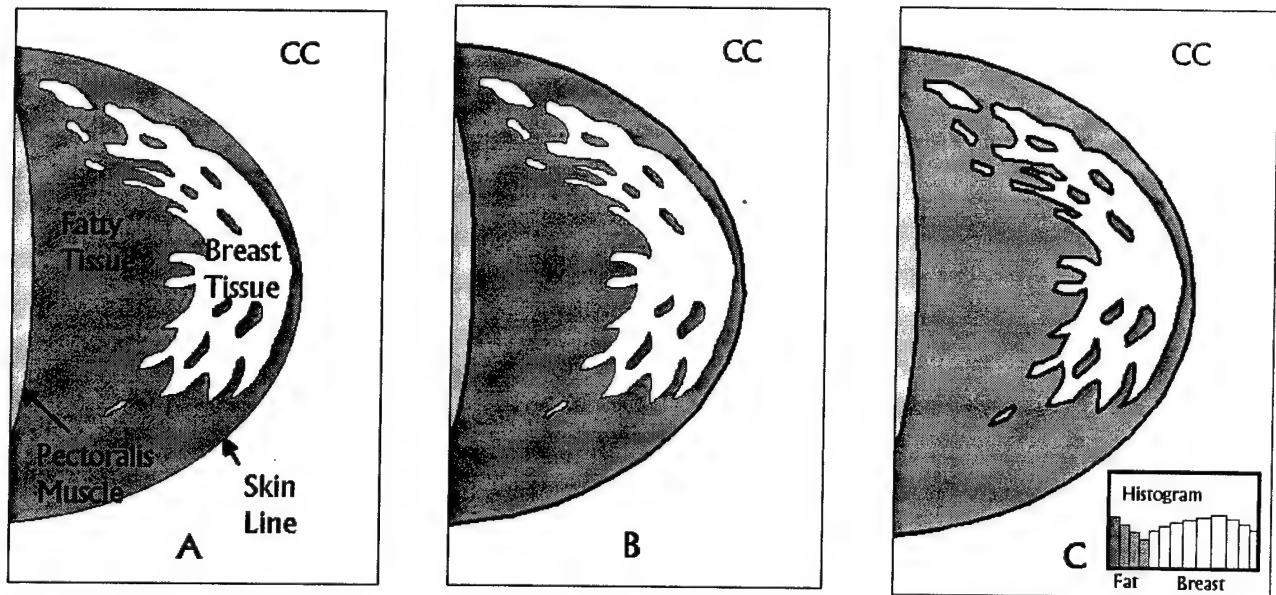


Figure 2. Percent change in density (mean, range) by quantitative assessment versus visual assessment.

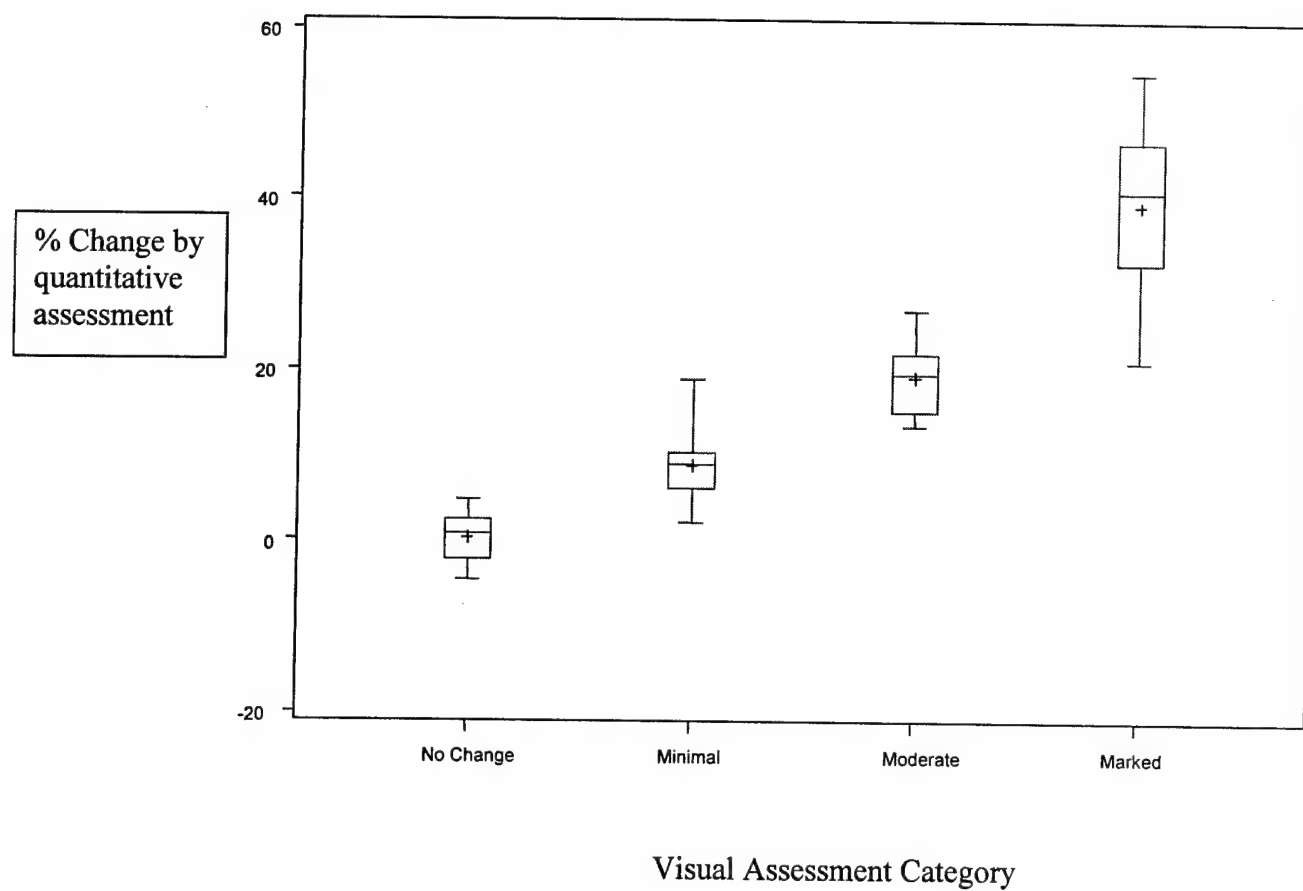


Table 1. Baseline characteristics of the study population

	HRT-associated Increase in Density (N = 51)	No Change in Density (N = 20)
Age (years) (mean, range)	59.6 (41 - 77)	60.3 (49 - 74)
Interval from baseline to index mammogram (months) (mean, range)	22.4 (11.5 - 59.6)	30.6 (12.4 - 59.3)
Baseline Parenchymal Pattern		
Fatty	9/51 (18%)	4/20 (20%)
Scattered	28/51 (55%)	7/20 (35%)
Heterogeneous	13/51 (25%)	8/20 (40%)
Extremely dense	1/51 (2%)	1/20 (5%)

Table 2. Quantitative assessment of increase in breast density with visual assessment of density change

Visual Change	Percent Change, mean (range)	20 th Percentile Difference	80 th Percentile Difference
No change	+0.2% (-4.6 - +4.7%)	-2.6	2.6
Minimal Increase	+8.8% (+2.0 - +18.8%)	5.8	10.5
Moderate Increase	+19.1% (+13.4 - +26.8%)	14.3	22.5
Marked Increase	+39.2% (+20.9 - +54.8%)	28.1	49.4

Table 3. Proposed scale of visual and quantitative assessment of change in breast density.

Visual Assessment	Proposed Quantitative Scale¹
No significant change	0 to 2.9%
Minimal Increase	3 to 14.9%
Moderate Increase	15 to 24.9%
Marked Increase	≥25%

¹ Percent increase in density

Table 4. Visual scale rating compared to proposed digital scale (number of cases (percent)).

	Proposed Quantitative Scale			
	0 to 2.9%	3 – 14.9%	15 – 24.9%	≥25%
Visual Scale				
No Change	18 (25.4%)	2 (2.8%)	0 (0%)	0 (0%)
Minimal Increase	1 (1.4%)	19 (26.8%)	1 (1.4%)	0 (0%)
Moderate Increase	0 (0%)	4 (5.6%)	10 (14.1)	2 (2.8%)
Marked Increase	0 (0%)	0 (0%)	1 (1.4%)	13 (18.3%)